8. (Amended) The method of claim 1 wherein said anti-hVEGF antibody consists of murine variable domains and human constant domains.

II. REMARKS

Claim Amendments

Claims 1, 8-10 are pending, of which claims 1 and 8 have been amended. Support for the amendments can be found, for example, in the specification at page 27, lines 25-31; page 41, lines 3-6 and 19-21 (for claim 1); and page 13, lines 6-10 (for claim 8). The amendments do not add new matter.

Rejections under 35 U.S.C. §112, first paragraph

Claim 8 remains rejected under 35 U.S.C. §112, first paragraph as allegedly containing unenabling subject matters. In particular, the enablement rejection relates to the term "chimeric" and the phrase "at least one constant chain domain is replaced." Claim 8 is also rejected as the specification allegedly does not contain a written description of the claimed invention. According to the Examiner, the limitations of "at least one constant chain domain" and "a chimeric murine antibody" lack clear support in the specification and the claims as originally filed.

In the interest of expediting the prosecution process, claim 8 has been amended. The amended claim 8 is directed to a method of using an anti-hVEGF antibody consisting of murine variable domains and human constant domains. Applicants submit that such antibodies are widely known and used in the art as "chimeric" antibodies, and are clearly described in the specification as "chimeric forms of murine antibodies" (page 13, lines 6-10). Since the amended claim 8 no longer recites "chimeric" or "at least one constant chain domain", the outstanding rejections under 35 USC 112, first paragraph are rendered moot and should be withdrawn.

Rejections under 35 U.S.C. §112, second paragraph

Claim 8 remains rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite because of the term "chimeric". Furthermore, claims 1 and 8-10 are rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite because of

the phrase "determining the degree of cerebral edema" in claim 1 and the term "homologous" in claim 8.

Applicants submit that the subject claims have been amended to more clearly define what is considered as the inventive subject matter. More specifically, claim 1 is directed to a method of reducing cerebral edema in a mammal by administering to the mammal an anti-hVEGF antibody in an amount effective to reduce the volume of cerebral edema. And claim 8 has been amended to remove recitation of the terms "chimeric" and "homologous". In view of the amendments to the claims, the basis for the rejections under 35 U.S.C. 112, second paragraph is believed to be overcome. Accordingly, Applicants respectfully request the rejections be withdrawn.

Rejections under 35 U.S.C. §102

Claims 1 and 8-10 remain rejected under 35 U.S.C. §102 as allegedly being anticipated by WO94/10202 for the reasons previously set forth in Paper No. 10, Section 10, pages 6-7. Applicants respectfully traverse.

The present invention encompasses methods of using a hVEGF antagonist comprising an anti-hVEGF antibody to reduce cerebral edema in the brain of a mammal. As disclosed in the specification and further discussed in Applicants' earlier response, the invention was based on the novel findings of VEGF's direct role in brain edema formation via increasing vascular permeability, and of the effective reduction of edema formation by administering a hVEGF antagonist. Accordingly, the invention as claimed is directed specifically to the reduction of cerebral edema in brain, regardless the state of particular diseases or disorders that may cause or accompany the edema.

Applicants respectfully disagree with the Examiner's contention that the claimed method is inherently anticipated by WO94/10202. As discussed in the background section of the specification and also in the previous response, the state of the art prior to the present invention was such that the direct role of VEGF in the formation of cerebral edema was unclear with contradictory experimental observations reported in the literature. Thus, it could not have been anticipated that an hVEGF antagonist would effectively reduce cerebral edema in the brain of a treated mammal.

Turing to the teachings of WO94/10202, Applicants point out the distinction between inhibiting tumor growth and reducing a pathological complication that may or may not accompany a particular tumor. VEGF has long been recognized for its important role in tumor angiogenesis, a process by which VEGF promotes formation of new blood vessels surrounding a tumor and providing nutrients for tumor growth. WO94/10202 teaches using anti-hVEGF antibody as an antagonist to block VEGF's angiogenesis activity, thereby inhibiting tumor growth *in vivo*. Such anti-angiogenesis methods are different from, and thus cannot anticipate, methods of reducing cerebral edema formation *in vivo*, which is directly associated with increased vascular permeability as opposed to angiogenesis.

The Example 4 of WO94/10202 was cited by the Examiner to support the anticipation rejection. As a matter of technical detail, Applicants respectfully point out that the *in vivo* results described therein, using xenograft mice transformed with various tumor cell lines (including a human glioma cell line), did not show reduction of cerebral edema in the host mice. Tumor cells were injected subcutaneously into the nude mice, and thus no cerebral edma formation or reduction thereof would have been observed.

Applicants submit that the claims are now in condition for allowance. An early Notice to that effect is respectfully requested. In the event that the Examiner wishes to discuss any aspect of this response or of the application, she is invited to contact the undersigned attorney directly. Applicants will be pleased to submit documents necessary to advance this application to issuance.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extension of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 07-0630. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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Date: September 7, 2001

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